EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA); Scientific Opinion on the Tolerable Upper Intake Level of calcium

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SCIENTIFIC OPINION

Scientific Opinion on the Tolerable Upper Intake Level of calcium [1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

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ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to re-evaluate the safety in use of calcium. The Panel was requested to consider if the Tolerable Upper Intake Level (UL) for calcium established by the SCF in 2003 (2,500 mg/day for adults, including pregnant and lactating women), which was based on different intervention studies of long duration in which total daily calcium intakes of 2,500 mg from both diet and supplements were tolerated without adverse effects, needed to be changed on the basis of new available evidence. A number of placebo controlled human intervention studies in adults published since then also showed that total daily calcium intakes of 2,500 mg from both diet and supplements are tolerated without adverse effects. The Panel considers that no relationship has been established between long-term calcium intakes from diet and supplements and increased risk of nephrolithiasis, cardiovascular disease or prostate cancer. No new data have become available which would require a revision of the UL for calcium for adults, including pregnant and lactating women, of 2,500 mg. No new data have become available which would allow the setting of a UL for infants, children or adolescents. Data from European populations indicate that intakes of calcium in high consumers among adult males can be close to the UL. Although available data do not allow the setting of a UL for infants, children or adolescents, no risk has been identified with highest current levels of calcium intake in these age groups.

KEY WORDS

Calcium, supplements, hypercalcaemia, hypercalciuria, UL, safety.

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SUMMARY

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to re-evaluate the safety in use of calcium and to provide, if necessary, revised Tolerable Upper Intake Levels (ULs) of calcium for all relevant population groups.

Calcium is important for the maintenance of healthy teeth and bones, cell signalling, coagulation, muscle contraction, neural transmission and many other functions. Calcium is the fifth most abundant element in the human body. Some 99 % of the total calcium of the body is located in bones and teeth, mostly as calcium hydroxyapatite. Bone mineral provides structure and strength to the body, and a reservoir of calcium that helps to maintain a constant concentration of calcium in the blood.

Foods vary widely in calcium content. The best sources are milk and milk products, which provide about 45 to 70 % of the dietary calcium in European diets. Some plants, drinking and mineral water, and food supplements are also good sources of well absorbable calcium.

A number of potential adverse effects of excessive calcium intakes have been proposed. These include hypercalciuria, deterioration of kidney function, kidney stone formation, the milk-alkali syndrome (MAS), vascular calcification, increased risk of cardiovascular disease and increased risk of prostate cancer.

The SCF (2003) based the derivation of a UL for calcium on the evidence of different intervention studies of long duration, some of which were placebo controlled, in which total daily calcium intakes of 2,500 mg from both diet and supplements were tolerated without adverse effects. Because of the abundance of data, the application of an uncertainty factor was considered unnecessary. A UL of 2,500 mg of calcium per day from all sources was proposed for adults, and for pregnant and lactating women.

A number of placebo controlled human intervention studies in adults published since then also show that total daily calcium intakes of 2,500 mg from both diet and supplements are tolerated without adverse effects.

The Panel notes that new case reports have become available on consumption of calcium supplements and the CAS/MAS syndrome. However, the Panel considers that no dose-response relationships can be derived from these.

The Panel considers that no relationship has been established between long-term calcium intakes from diet and supplements and increased risk of nephrolithiasis, cardiovascular disease or prostate cancer.

The Panel concludes that no new data have become available which would require a revision of the UL for calcium for adults, including pregnant and lactating women, of 2,500 mg, and that no new data have become available which would allow the setting of a UL for infants, children or adolescents.

Data from European populations indicate that intakes of calcium in high consumers among adult males can be close to the UL. Although available data do not allow the setting of a UL for infants, children or adolescents, no risk has been identified with highest current levels of calcium intake in these age groups.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Calcium has been assessed in the past by the Scientific Committee on Food. In the Opinion on the Tolerable Upper Intake Level (UL) of calcium of 4 April 2003 an UL was established for adults of 2500mg of calcium per day for calcium intake from all sources. The Committee could not derive an UL for children and adolescents due to insufficient data.

On 30 November 2010, the American Institute of Medicine (IoM) published a report on "*Dietary Reference Intakes for Calcium and Vitamin D*". In this report, the IoM proposes new reference values and UL values for calcium which, as stated in the report "*are based on much more information and higher-quality study results than were previously available*".

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to:

- re-evaluate the safety in use of calcium,
- if necessary, provide revised tolerable upper intake levels, that are unlikely to pose a risk of adverse health effects, for calcium for all relevant population groups.

ASSESSMENT

1. Introduction

Calcium is important for the maintenance of healthy teeth and bones, cell signalling, coagulation, muscle contraction, neural transmission and many other functions. Calcium is the fifth most abundant element in the human body. Some 99 % of the total calcium of the body is located in bones and teeth, mostly as calcium hydroxyapatite. Bone mineral provides structure and strength to the body, and a reservoir of calcium that helps to maintain a constant concentration of calcium in the blood.

In 2003, the Scientific Committee on Food (SCF) established a Tolerable Upper Intake Level (UL) of calcium for adults, including pregnant and lactating women, of 2,500 mg/day. This UL was based on different long-term intervention studies in which a total daily intake of 2,500 mg of calcium/day from all sources (diet and supplements) was tolerated without adverse effects. The Committee was unable to derive a UL for children and adolescents from the very few data available from intervention studies, and it was considered inappropriate to derive such age-specific ULs via extrapolation from data collected in older age groups.

The UL for calcium of the SCF (2003) was the same as that from the US Institutes of Medicine (IoM, 1997), which was based on a LOAEL of 4,000-5,000 mg/day identified by using the milk alkali syndrome as the critical endpoint and applying an uncertainty factor of 2 because of observed associations between calcium intake and the potential hazard of kidney stones, hypercalciuria, and interference of dietary calcium with the bioavailability of some minerals in vulnerable populations. The IoM also defined the same UL of 2,500 mg of calcium/day for adults >70 years of age, for children and adolescents 1-18 years of age, and for pregnant and lactating women, but could not establish a UL for infants.

In 2011, the IoM published its re-assessment of the UL for calcium, which for adults ≥51 years old was based on a LOAEL of 2,000 mg of calcium/day with nephrolithiasis as the critical endpoint (Jackson et al., 2006). No uncertainty factor was applied. For adults 19 to 50 years of age, the UL was the same as in 1997 and was derived by interpolation between the UL for older adults and the new UL of 3,000 mg for children aged 9-13 years and adolescents aged 14-18 years. This latter value was set taking into account a presumably higher need of, and consequently a higher tolerance for, calcium in the age group 9-18 years in connection with the pubertal growth spurt. A UL of 1,500 mg of calcium/day was derived from a NOAEL of 1,750 mg/day observed in one intervention study on infants aged 2.5 to 5 months at baseline and 9 months at the end of the intervention (Dalton et al., 1997; Sargent et al., 1999). Uncertainty factors of 2 and 1.2 were applied to adjust for the weight increment during the intervention and the results were rounded up to ULs of 1,000 mg/day for infants aged 0-6 months and of 1,500 mg/day for infants aged 6-12 months, respectively. No new data were available for the age group 1-8 years and the UL of 2,500 mg/day was kept. For pregnant and lactating women, the age-specific UL for adolescents aged 14-18 years of 3,000 mg/day and the UL of 2,500 mg/day for women >19 years of age were considered adequate.

The Panel was requested to consider whether the UL for calcium established by the SCF in 2003 needed to be changed on the basis of new available evidence.

2. Dietary Intake

2.1. Food sources including dietary supplements

Foods vary widely in calcium content. The best sources are milk (120 mg/100 g) and milk products (up to about 1,100 mg/100 g), from which about 32 % of calcium is absorbable (Weaver, 2001). In

European diets, about 45 to 70 % of the dietary calcium intake is provided by dairy products (Guéguen and Pointillart, 2000; IUNA (Irish Universities Nutrition Alliance), 2001). Some plants are good sources of well absorbable calcium, for example brassica, almonds and dried apricots. However, some vegetables (rhubarb, spinach) contain considerable amounts of calcium which is poorly absorbed because of a high content in oxalate, which forms sparingly soluble calcium oxalate. Drinking water and mineral waters (>150 mg calcium/L) can also be good sources of absorbable calcium.

In the European Union, the following forms of calcium are authorised for addition to foods and for use in food supplements (Annex II of the Regulation (EC) No 1925/2006[4] and Annex II of Directive 2002/46/EC[5]): carbonate, chloride, citrate malate, gluconate, glycerophosphate, lactate, hydroxide, oxide, acetate, L-ascorbate, bisglycinate, salts of citric acid, pyruvate, salts of orthophosphoric acid, succinate, L-lysinate, malate, L-pidolate, L-threonate, sulphate.

2.2. Dietary intakes

Mean intakes of calcium in European countries vary according to sex, age, and supplementation habits (Appendices A and B). There is a large diversity in the methodology used to assess the individual intakes of children, adolescents and adults. These differences in dietary assessment methods make direct comparisons difficult. Data from Poland based on a single 24-h recall have been listed in Appendices A and B for completeness, but have not been considered in the text. Age classifications may not be uniform and comparability is also hindered by differences in food composition tables used for the conversion of food consumption data to nutrient intake data (Deharveng et al., 1999). Although these differences have an impact on the accuracy of between-country comparisons, the data presented give a rough overview of average calcium intakes and intakes in high consumers in a number of European countries.

2.2.1. Adults

Mean calcium intakes from food only were between 623 mg/day (Belgium, ≥75 years) and 1,374 mg/day (Denmark, men, 18-24 years), and median intakes were within this range. Available values for high percentiles of intake were between 1,045 mg/day (Spain, P95, women, 18-64 years) and 2,422 mg/day (Germany, P95, men, 19-24 years). Mean calcium intakes in the surveys considering food and food supplements combined were within these ranges, as well as values for the highest percentiles of calcium intake.

2.2.2. Infants (≤1 year)

Mean calcium intakes from food were available from one country only (The Netherlands) and varied between 730 mg/day (0.75 years) and 824 mg/day (1 year). The value for the high percentile was 1,085 mg/day (P90, 1 year). Mean calcium intakes for the entire sample and for the highest percentiles of consumption in the only study (Finland) which considered food and food supplements together were within these ranges.

2.2.3. Children (generally between 1 and 14 years)

For young children (0-3 years), mean calcium intakes from food were between 664 mg/day (Italy, 0-<3 years) and 1,024 mg/day (Greece, 1-5 years). Values for the high percentiles of calcium intake

[4] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. OJ L 404, 30.12.2006, p. 26-38.
[5] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12.7.2002, p. 51-57.

were between 1,070 mg/day (Italy, P95, 0-3 years, including fortified food) and 1,392 mg/day (Greece, P90, 1-5 years). Mean calcium intakes for the entire sample and for the highest percentiles of consumption in the surveys considering food and supplements together were within these ranges.

For older children (about 3-14 years) mean calcium intakes from food were between 804 mg/day (Ireland, girls, 5-12 years; United Kingdom, 4-10 years) and 1,072 mg/day (Denmark, aged 4-14 years), and median intakes were within that range. Values for the high percentiles of intake were between 1,123 mg/day (Spain, P95, 4-10 years) and 1,776 mg/day (Denmark, P95, 4-14 years). Calcium intakes were slightly higher in food surveys considering food and food supplements together. In these surveys, mean calcium intakes were between 724 mg/day (The Netherlands, 4-6 years) and 1,103 mg/day (Finland, boys, 6 years), and median intakes were within that range. Values for the high percentiles of intake varied between 1,151 mg/day (Spain, P95, 4-10 years, including fortified food) and 1,623 mg/day (The Netherlands, P95, boys, 9-13 years).

2.2.4. Adolescents (generally between 10 and 18 years)

Mean calcium intakes from food varied from 734 mg/day (Ireland, girls, 13-17 years) to 1,337 mg/day (Germany, 12-17 years). The two available median values were within that range. Values for the high percentiles of intake varied between 1,231 mg/day (Spain, P95, 11-17 years) and 2,400 mg/day (Germany, P95, 12-17 years).

Mean calcium intakes from food and supplements combined were between 786 mg/day (United Kingdom, 11-18 years) and 1,396 mg/day (Germany, 12-17 years, including fortified food). Available median intakes were within that range. The values for the high percentiles varied between 1,267 mg/day (Spain, P95, 11-17 years, including fortified food) and 2,515 mg/day (P95, Germany, 12-17 years, including fortified food).

3. Hazard identification

3.1. Calcium physiology and homeostasis

Calcium homeostasis is under endocrine and genetic control. Systemic and local factors regulate intestinal absorption, influx and efflux from bone, and calcium excretion and re-absorption by the kidney. Because of this regulatory network, there is no biomarker for calcium status.

3.1.1. Serum calcium and its regulation

Calcium is present in the blood in three different forms: as free Ca^{2+} ions, bound to protein (about 45 %), and complexed to citrate, phosphate, sulphate and carbonate (about 10 %). Calcium in the blood (and in extracellular fluid) is kept constant at 2.5 mmol/L (range 2.25-2.6 mmol/L), but it is ionised calcium (between 1.1-1.4 mmol/L) which is controlled by the interrelated action of three hormones, namely parathyroid hormone (PTH), 1,25-dihydroxycholecalciferol (1,25-$(OH)_2$-D) and calcitonin. The first two determine how much Ca^{2+} moves out of or into the body, whilst PTH determines how Ca^{2+} moves between the extracellular fluid and bone.

A decrease in serum concentrations of Ca^{2+} induces the release of PTH via the calcium-sensing receptor (CaSR) which is located on the cell surface of the parathyroid glands. The PTH stimulates 1,25-$(OH)_2$-D synthesis in the kidney, bone resorption, and renal re-absorption of calcium (Perez et al., 2008). Synthesis of 1,25-$(OH)_2$-D is also stimulated by low serum phosphorus concentrations and decreases with high phosphorus concentrations. An increase in serum concentrations of Ca^{2+} inhibits PTH secretion via the CaSR and 1,25-$(OH)_2$-D synthesis, and stimulates calcitonin secretion by the parafollicular C cells of the thyroid gland. Other locations of the CaSR include the intestine, kidney,

thyroid gland, lung, brain, skin, bone marrow, and osteoblasts. According to population-based genome-wide association studies, individual serum calcium concentrations within the normal range are influenced by some single-nucleotide polymorphisms of the CaSR gene (O'Seaghdha et al., 2010; Riccardi and Brown, 2010).

Several genetic disorders have been described where this homeostatic regulation is disturbed and hypercalcaemia results. The latter is considered to be a consequence of either due to loss-of-function mutations of CYP24A1 which encodes 25-hydroxyvitamin D 24-hydroxylase leading to idiopathic infantile hypercalcaemia (OMIM 143880) , or inactivating mutations of the CaSR gene (Schlingmann et al., 2011). Such mutations can result in either neonatal severe primary hyperparathyroidism (OMIM 239200) or familial hypocalciuric hypercalcaemia (OMIM 145980). Rarely, inactivating auto-antibodies against CaSR cause hypocalciuric hypercalcaemia (Riccardi and Brown, 2010). Activating mutations of the CaSR gene can be the cause of autosomal dominant hypoparathyroidism (OMIM 601298) with hypocalcaemia and hypercalciuria, or of the Bartter syndrome type V.

Hypercalcaemia is defined by serum calcium concentrations >2.75 mmol/L (11 mg/dL). Values used for the diagnosis of hypercalcaemia may change across laboratories and will be defined in this Opinion according to the cut-off selected by the authors in each individual study. The most common causes of hypercalcaemia include malignant tumours, hyperparathyroidism of different aetiology, and less frequently excessive calcium and/or vitamin D intakes. Clinical symptoms of persistent hypercalcaemia are fatigue, muscular weakness, anorexia, nausea, vomiting, constipation, tachycardic arrhythmia, soft tissue calcification, failure to thrive and weight loss. Hypercalcaemia can lead to hypercalciuria when the renal capacity of calcium re-absorption is exceeded, and to renal concentration defects resulting in polyuria through activation of the renal CaSR.

Consequences of severe chronic hypercalcaemia are nephrolithiasis and impairment of kidney function, resulting in loss of the concentrating ability of the kidney (i.e., a decrease in salt and water reabsorption), and in volume and salt depletion. Chronic hypercalcaemia may also lead to calcification of soft tissues (e.g., nephrocalcinosis and vascular calcification), particularly when phosphorus concentrations in the blood are also high, as in renal insufficiency. The age-related decrease in urinary calcium excretion and renal function increases the sensitivity of older people to excess calcium intakes.

3.1.2. Calcium absorption in the intestine

Calcium must be in a soluble form or bound to soluble organic molecules to be absorbable. Depending on solubility, chemical form and other factors of the food, the fractional absorption of dietary calcium in adults is around 25 % (range 10 to 40 %). Fractional absorption decreases with high calcium content of diets and increases with low-calcium diets. This adaptation is modulated by PTH and 1,25-$(OH)_2$-D in response to lower or higher serum calcium concentrations. Fractional calcium absorption is highest (up to 60%) in infancy (Abrams et al., 1997), declines thereafter to rise again before puberty, and declines after puberty to the adult value of 25 %. During pregnancy calcium absorption is twice as high (Moser-Veillon et al., 2001). Dietary factors also modulate calcium absorption. Most calcium salts used in fortified foods or dietary supplements are absorbed to a similar extent as calcium from dairy foods. A difference in the kinetics of calcium taken as a supplement and calcium taken with food is manifested in earlier and higher rises of serum calcium with supplemental calcium than with calcium ingested with food, whilst the total amount of calcium absorbed may be enhanced with food (Heaney et al., 1989). Significant differences in the time course of rises in serum calcium and reactive decreases in serum PTH concentrations following the consumption of different calcium salts (formate >> citrate > carbonate) in the fasting state have been observed (Hanzlik et al., 2005). The clinical significance with respect to calcium uptake into bone and excretion of excess calcium into urine is not clear. Ionised calcium in serum following the ingestion of 1,000 mg of calcium as a supplement just before a meal by healthy subjects rose in 20 of 40 trials above the upper

limit of normal (specified as 1.28 mmol/L) within two to four hours, and was accompanied by a significant increase in calcium excretion in the urine and by an increase of the calcium/creatinine ratio by up to 0.13 (Reid et al., 1986). This finding indicates that rapidly absorbed calcium can transitorily lead to increased concentrations of serum and urinary calcium. The bulk of unabsorbed calcium forms complexes with bile acids, free fatty acids, oxalic acid and phytic acid, and excreted in the faeces (Heaney, 2002).

There are two main mechanisms for calcium transport in the intestine: an active transcellular process and a passive paracellular process. Both are regulated by hormones, nutrients and other factors.

Active transcellular transport in the small intestine is saturable and regulated by dietary intake and the needs of the body. The efficiency of this transport improves with diets low in calcium and in situations of increased need for calcium (e.g. growth, pregnancy and lactation), and it decreases with age. Regulation of the uptake of calcium ions (Ca^{2+}) at the apical side of the epithelium, and the release at the basolateral membrane, involves epithelial Ca^{2+} channels TRPV5 and TRPV6 (which are also expressed in the kidney and other organs), calbindins, the plasma-membrane Ca-ATPase (PMCA), and the Na^{+}/Ca^{2+} exchanger (NCX1), whose activation and/or expression is under the control of 1,25-$(OH)_2$-D by binding to the vitamin D receptor (VDR).

Passive para-cellular diffusion through the tight junctions of the intestinal epithelium, particularly of the jejunum and ileum, follows down an electrochemical gradient together with water, sodium and glucose, which is determined by the concentration of soluble calcium in the gut lumen. Passive para-cellular diffusion becomes important when dietary calcium is high and the trans-cellular pathway is down-regulated. This process is independent of age (Bronner, 1992).

3.1.3. Renal excretion and re-absorption of calcium

The majority of calcium absorbed is stored in the skeleton. Excess of absorbed calcium is excreted in urine, faeces and sweat. Calcium balance is positive in healthy children, adolescents and young adults before bone growth and bone modelling cease. Renal calcium excretion is the net result of glomerular filtration and tubular passive (collecting duct) or active (proximal tubule, loop of Henle, distal tubule) reabsorption (normal over 98 % of the filtered load). Active transport is under the control of PTH, calcitonin and 1,25-$(OH)_2$-D, the levels of which are set via the CaSR by the calcium concentrations in extracellular fluid (Hoenderop et al., 2002). Average 24-h excretion of calcium is 40 mg in young children, 80 mg in prepubertal children and reaches about 150-200 mg in healthy adults. Small changes in the levels of Ca^{2+} which is filtrated into the urine can lead to substantial changes in urinary calcium. Below a serum calcium concentrations of 2 mmol/L, little (if any) calcium is excreted in the urine (<30 mg/24 h). The maximum amount of calcium which can be excreted by healthy humans is about 1,000 mg/24 h. Higher amounts are associated with the risk of calcium deposition in the renal tissue or with the formation of kidney stones because urine is supersaturated with calcium and phosphate. Stone formation and renal calcification are enhanced by an alkaline environment.

Urinary calcium excretion is increased by dietary sodium intake (30 to 40 mg of calcium excreted per every two grams of dietary sodium) (Matkovic et al., 1995) and in chronic metabolic acidosis (Bushinsky, 2001). Calcium excretion rises with excess dietary protein intake (by 0.5 mg for each gram of dietary protein, when intake is >47 g/day) (Walker and Linkswiler, 1972; Whiting et al., 1998).

Hypercalciuria is defined by a calcium excretion >0.3 mg/mg creatinine in 24-hour urine of adults, by a calcium excretion >250 mg/day in women and >275-300 mg/day in men, or by a calcium excretion >4 mg/kg bw/day for both men and women. Calcium/creatinine ratios in urine are higher in infancy and decrease with age. In randomly collected urine samples, calcium/creatinine ratios of 0.9, 0.6, 0.42 and 0.22 have been reported for ages <7 months, 7-18 months, 19 months to 6 years, and adults,

respectively (Sargent et al., 1993). Calcium/creatinine ratios may differ somewhat in different populations because of differences in dietary habits, sunshine exposure, drinking water composition and ethnicity. An increase in the calcium/creatinine ratio in a random urine sample can be an incidental occurrence only.

Chronic hypercalciuria may be the consequence of increased intestinal absorption of calcium (absorptive) or of decreased renal calcium reabsorption (resorptive). Causes of chronic hypercalciuria include excessive calcium intake (without accompanying hypercalcaemia), excessive vitamin D intake, hyperparathyroidism, hyperthyroidism, renal tubular acidosis, sarcoidosis or malignant tumors. Idiopathic (primary) hypercalciuria is characterised by the lack of concomitant hypercalcaemia. Pregnant women are often hypercalciuric from the 12th gestational week onwards even with "normal" calcium intakes. The hypercalciuria results from the doubling of intestinal calcium absorption in early pregnancy, which leads to positive calcium balance (Heaney and Skillman, 1971).

Persistent hypercalciuria is associated with decreased bone mineral density and higher risk of kidney stone formation, particularly in subjects with idiopathic hypercalciuria (Audran et al., 1991; Bataille et al., 1991). Kidney stones affect more than 5 % of the population in Europe, and up to 20-40 % of patients with calcium containing stones (about 80 % of kidney stones) have idiopathic hypercalciuria. As stones form in urine that is supersaturated, high concentrations of calcium (and oxalate) in urine, rather than the total amount of calcium excreted, increase the risk of nephrolithiasis (kidney stones). Other dietary risk factors for nephrolithiasis include low fluid intakes and high intakes of protein, salt, sucrose, alcohol and oxalate. Pregnancy is associated with an increased risk of kidney stone formation.

3.2. Adverse effects of excess calcium intake

A number of potential adverse effects of excessive calcium intakes have been proposed. These include hypercalciuria, deterioration of kidney function, kidney stone formation, the milk-alkali syndrome (MAS), vascular calcification, increased risk of cardiovascular disease and increased risk of prostate cancer (IoM, 2011).

3.2.1. Milk-alkali syndrome/calcium-alkali-syndrome

The adverse effects of combined therapy for peptic ulcers with milk and absorbable antacids (mostly sodium bicarbonate or calcium carbonate) were named collectively MAS (Burnett et al., 1949; Cope, 1936). Milk-alkali syndrome is characterised by metabolic alkalosis and hypercalcaemia with dehydration, renal failure, nephrocalcinosis and nephrolithiasis in variable combinations and severity. The SCF (2003) compiled case reports from 82 patients (24-95 years) with MAS, in which total calcium intakes were generally inadequately documented but reported to range between 400 and 23,000 mg/day. Milk-alkali syndrome was not observed in the course of a number of intervention studies which involved between 11 and 2,295 individuals (children, pregnant and pre- or perimenopausal women, elderly subjects), tested the effects of calcium supplements (500 to 2,000 mg/day) on different outcomes, and lasted between 12 weeks to four years (SCF, 2003).

Since then the therapy including milk for peptic ulcers has become obsolete but the syndrome has been increasingly observed with high intakes of supplemental calcium carbonate and MAS has been re-named calcium-alkali-syndrome (CAS) (Patel and Goldfarb, 2010). On the basis of 14 cases (2004-2010) reporting elevated serum calcium (2.64-6.43 mmol/L) and creatinine concentrations in males and females (35-81 years) consuming calcium carbonate at doses >1,000-44,000 mg/day, the IoM (2011) concluded that supplemental intakes of calcium carbonate ≥3,000 mg/day were hazardous. Duration of supplementation was only reported in seven cases (from weeks to 19 years).

Extensive calcification of renal convoluted tubular cells and the tubular lamina have been described in kidney biopsies of patients with MAS or CAS, and which in severe cases were associated with interstitial fibrosis, areas of inflammatory changes and peri-glomerular fibrosis. The extent of calcium deposition was proportional to renal dysfunction. Calcium deposits in the cornea and conjunctiva, and less commonly in peri-articular tissue, subcutaneous tissue, the central nervous system, liver, adrenal glands, bone and lungs, have also been observed in chronic cases of MAS (Medarov, 2009).

The Panel notes that supplemental alkaline calcium intakes at doses >1,000 mg/day may increase the risk of CAS, but these case reports do not allow an estimation the amount of calcium or the duration of the treatment at which the risk increases.

A decrease in calcium excretion or in kidney function (e.g. in old age), an increase in calcium re-absorption (e.g. thiazide diuretics), or conditions leading to metabolic alkalosis (e.g. hyperemesis in pregnancy or bulimia) are risk factors for developing CAS when individuals are taking alkaline calcium supplements (Medarov, 2009).

3.2.2. Hypercalciuria, kidney function and kidney stones

3.2.2.1. Adults

The SCF (2003) reported on a higher frequency (compared to placebo) of incidental hypercalciuria (>350 mg/day) in post-menopausal women consuming calcium supplements (1,600 mg/day), in addition to dietary calcium intakes of about 800 mg/day, for four years. No subject receiving calcium supplements developed kidney stones, nephrocalcinosis or a reduction in glomerular filtration rate (Riggs et al., 1998). A trend for an increase in serum creatinine (by 1.2 µmol/L) with total calcium intakes of 2-3 g/day had been observed in a study involving 130 peri-menopausal women (Elders et al., 1994), whereas no effect was reported in 46 women aged 50-70 years at comparable calcium intakes (Schaafsma et al., 2002). It was unclear whether compromised glomerular function as indicated by increases in serum creatinine could have been attributed to high calcium intakes in the first study.

The effect of different doses of calcium on hypercalciuria and/or kidney function has not been systematically investigated, and no new data have become available since 2003.

The SCF (2003) also reported no increased risk of kidney stones in approximately 5,000 subjects (from different intervention studies) who received between 500 and 2,000 mg calcium/day as a supplement in addition to 300 to 1,800 mg of calcium/day from the diet (total intakes between 1,300 and 3,000 mg calcium/day) during three months to four years. None of these studies were designed to investigate the effects of calcium supplements on kidney stone formation. In two prospective cohort studies with 45,619 men aged between 40 and 75 years followed over four years (the Health Professionals Follow-up Study, Curhan et al., 1993) and 91,731 women aged between 34 and 59 years followed over 12 years (the Nurses' Health Study I, Curhan et al., 1997), without kidney stones at the beginning of the observation period, total calcium intakes >1,050 mg/day in men and >1,100 mg/day in women decreased the risk of kidney stone formation by approximately 35 % compared to lower intakes. In both studies, an inverse association was reported between dietary calcium and risk of kidney stones after adjustment for confounders, whereas calcium supplements in daily amounts below 100 mg increased the risk for stone formation by 20 % in women, with no further increase in the relative risk at higher intakes. In a population-based study which involved 1,309 women aged 20 to 92 years, women with kidney stones (n=44) ingested on average 250 mg less calcium per day than women without stones (840 *vs* 1,070 mg/day). Calcium supplements were not associated with the risk of kidney stone formation (Sowers et al., 1998).

The SCF (2003) concluded that both observational studies on the relationship between total calcium intake and kidney stone incidence and intervention studies with calcium supplements did not allow an estimation of the calcium intake on a population basis which would promote kidney stone formation.

A longer follow-up of the Health Professionals Study (Taylor et al., 2004) and results from a new Nurses' Health Study II (Curhan et al., 2004) have been published since then. In addition, the IoM (2011) established the UL for adults aged >51 years (LOAEL of 2,000 mg of calcium/day with nephrolithiasis as the critical endpoint) on the basis of a secondary analysis of the Women's Health Initiative (WHI) intervention trial (Jackson et al., 2006), for which a subsequent publication has become available (Wallace et al., 2011).

In the 14-year follow-up of the Health Professionals Study (Taylor et al., 2004), self-administered food frequency questionnaires (FFQs) were used to assess dietary (and supplemental) intakes at baseline and every four years in 45,619 men aged 40 to 75 years without history of nephrolithiasis. A total of 1,473 incident symptomatic kidney stones were documented. After adjusting for relevant risk factors, a higher dietary calcium intake was associated with a reduced risk of kidney stones (RR 0.69, 95 % CI 0.56-0.87, for men in the highest *vs.* the lowest quintile of calcium intake) in men aged <60 years. Median calcium intakes from the diet were 503 mg/day in the lowest and 1,194 mg/day in the highest quintiles, respectively. There was no association between dietary calcium and stone formation in men aged ≥60 years. Supplemental calcium intake was not associated with risk of developing kidney stones.

Similarly, in the eight-year follow-up of the Nurse's Health Study II (Curhan et al., 2004), self-administered food frequency questionnaires were used to assess dietary (and supplemental) intakes at baseline and at four years of follow-up in 96,245 female participants aged 27 to 44 years with no history of kidney stones. A total of 1,223 incident symptomatic kidney stones were documented. After adjusting for relevant risk factors, a higher dietary calcium intake was associated with a reduced risk of kidney stones (RR 0.73, 95 % CI 0.59-0.90, for women in the highest *vs.* the lowest quintile of calcium intake). Calcium intakes from diet were <626 mg/day in the lowest and >1,129 mg/day in the highest quintiles, respectively. Supplemental calcium intake was not associated with risk of kidney stone formation.

The Panel notes that dietary calcium intakes in the range of the most recent dietary recommendations do not promote kidney stone formation on a population basis. The Panel also notes that calcium supplements have not been associated with an increased risk of kidney stones in large prospective cohort studies.

In the Women's Health Initiative trial (Jackson et al., 2006), 36,282 post-menopausal women aged 50 to 79 years (mean age 62 years) were randomly assigned to consume with meals either a placebo (n=18,106) or 1,000 mg of elemental calcium (calcium carbonate) with 10 µg (400 IU) of vitamin D_3 per day (n=18,176) for an average period of seven years. Hypercalcaemia and kidney stones were among the exclusion criteria. The primary outcomes were bone fractures and measures of bone density. Subjects were allowed to continue the use of personal supplements up to 1,000 mg of calcium and up to 12.5 µg of vitamin D per day. Mean baseline intake (diet and non-trial supplements) of calcium was approximately 1,150 mg/day, and mean baseline intake of vitamin D was about 9 µg/day. About 40 % of the subjects consumed >1,200 mg calcium/day at baseline and 29 % consumed personal supplements with >500 mg calcium daily. Compliance (≥80 % of the assigned study supplements) ranged from 60 % to 63 % during the first three years of follow-up, with an additional 13 % to 21 % of the participants taking at least half of their study pills. At the end of the trial, 76 % of the women were still taking the study supplements, of which 59 % were compliant. Dietary calcium intake during the trial remained stable, but intake from supplements increased by 100 mg/day in both groups. Supplementation with calcium and vitamin D resulted in an increased risk (17 %) of self-reported clinically diagnosed kidney stones. Kidney stones were reported by 449 women in the supplemented group, as compared to 381 women in the placebo group (hazard ratio, 1.17; 95 %

CI 1.02-1.34). The Panel notes that although excluded by protocol design, 161 participants in the active arm and 172 in the placebo arm had a self-reported history of urinary tract stones and were included in the intention-to-treat analysis. It is unclear whether (and the extent to which) women with history of kidney stone formation contributed to the cases in each group. In a further analysis of the same study (Wallace et al., 2011), neither total calcium intake nor the use of calcium supplements at baseline were associated with the risk of kidney stones. The risk of kidney stones was not significantly different between the treatment and placebo groups when only subjects compliant with the study treatments were considered (hazard ratio: 1.21; 95 % CI 0.98-1.34). Confirmation of diagnosis upon hospital admission occurred in a small proportion of women (35 cases in each group) and was not significantly different between groups. The Panel notes that this study did not assess the relationship between dietary, supplemental (sum of both personal and trial supplements) or total calcium intakes in relation to the risk of kidney stone formation, but rather the effect of an additional amount of calcium (and vitamin D) over widely variable baseline calcium intakes from food and personal supplements (from <400 mg/day to >1,490 mg/day), and this additional amount of calcium was unrelated to the risk of developing kidney stones. The Panel also notes that additional calcium (and vitamin D) supplementation did not increase the risk of self-reported kidney stones in subjects who complied with the study treatment, or the proportion of women with objective diagnosis of kidney stones requiring hospital admission. The Panel considers that this study does not provide evidence for an increased risk of kidney stones which could be attributed to high calcium intakes.

The Panel notes that calcium intakes up to about 2,400 mg/day have not been associated with an increased risk of chronic hypercalciuria or impaired kidney function, and that calcium intakes up to 3,000 mg/day have not been associated with an increased risk of nepholithiasis in the general adult population.

3.2.2.2. Infants

One intervention study assessed calcium excretion in urine and renal function in relation to calcium intakes in infants. The formation of kidney stones in infants is rare.

A double-blind RCT (Dalton et al., 1997; Sargent et al., 1999) was performed to investigate the efficacy of an iron-fortified (12.8 mg/L) cow's milk-based formula with added calcium glycerophosphate (1,800 mg calcium/L, 1,390 mg phosphorus/L) *vs.* the same (control) formula without added calcium and phosphate (calcium 465 mg/L and phosphorus 317 mg/L) on the prevention of lead absorption in infants. The effects of the study formulas on calcium and iron metabolism were also assessed among other indicators of safety. Eligibility was tested pre-randomisation in 314 formula-fed healthy infants who consumed the test formula during a one-month run-in phase. Three infants developed hypercalciuria (calcium/creatinine >0.8 mg/mg) and were excluded from randomisation for this reason. A total of 103 eligible infants aged 3.5-6.0 months were randomised to consume either formula for nine months. Blood samples were obtained at baseline and at four and nine months, and urine samples at baseline, one, two, four, six and nine months for calcium and creatinine analysis. At the end of the intervention the mean age of the children was 14 months. Eleven children dropped out in each of the study groups for various reasons. Calcium intake from formula was five times higher in the intervention group (n=41) than in controls (n=40) at baseline and at four and nine months (1,740±450, 1,710±460 and 1,560±700 mg/day *vs* 480±90, 400±130 and 340±173 mg/day, respectively). Serum calcium concentrations did not differ between groups. One child in the control formula group had a serum calcium concentration >2.72 mmol/L after four months which returned to normal after nine months. There were no significant differences in urinary calcium/creatinine ratios between groups at baseline, or at four or nine months. Incidental hypercalciuria was observed in five infants in each group, which only persisted in a repeat sample in one subject of each group. Haematuria was not observed in any subject.

The Panel notes that in one small study, dietary calcium intakes up to about 1,750 mg/day for nine months did not increase the risk of hypercalcaemia, clinically significant hypercalciuria, or symptoms of kidney stones in infants.

3.2.2.3. Children and adolescents

In 2003, the SCF (2003) noted that no adverse effects of calcium citrate-malate supplements (500 to 1,000 mg calcium over 1.5 to 3 years) or of extra dairy foods or foods fortified with milk extracts (700 to 820 mg/day extra calcium over one year) were reported in 217 children (from five intervention studies) between 6 and 14 years and between 6.6 and 11 years, respectively, in comparison to non-supplemented controls. Mean calcium intakes from diet in groups receiving calcium supplements were about 900-1,000 mg/day. The SCF considered these data as insufficient to derive a UL for children or adolescents.

In a double-blind RCT aimed at investigating the role of calcium supplementation on lead poisoning, 88 "moderately poisoned" children aged 1-6 years were randomised to consume calcium (dose adjusted to reach 1,800 mg/day from food and supplements) or placebo for three months. Data from 67 children were available for analysis (35 in the calcium group). Calcium intake at enrolment was 1,108±465 mg and 973±409 mg for the placebo controls and supplemented groups, respectively. Urinary calcium/creatinine ratios did not differ between children in the intervention (total calcium intake of 1,701±121 mg /day) and control (1,012±454 mg Ca/day) groups, and were 0.1±0.1 throughout the study. Haematuria was not observed (Markowitz et al., 2004).

The Panel notes that, in one small study of short duration, calcium intakes of about 1,800 mg/day for three months did not affect renal function in children aged 1-6 years. No new data are available for adolescents.

3.2.3. Risk of cardiovascular disease

Chronic hypercalcaemia can lead to calcification of soft tissues, particularly if phosphorus levels are also high, but no relationship between calcium intake and the occurrence of nephrocalcinosis or calcification of vascular tissue has been established in humans except in the presence of decreased kidney function. Coronary artery calcification has been described in patients with renal insufficiency on dialysis and treated with calcium-containing phosphate binders (Asmus et al., 2005; Block et al., 2005; Goodman et al., 2000; Russo et al., 2007), but not in healthy subjects.

It has been hypothesised that excess calcium intakes leading to chronic hypercalcaemia could increase the risk of cardiovascular events through arterial calcification. Arterial calcification has been associated with an increased risk of cardiovascular morbidity and mortality in men and women in a number of prospective cohort studies (Jacobs et al., 2010; Levitzky et al., 2008; Wilson et al., 2001; Wong et al., 2009).

Few studies have investigated the relationship between calcium intake and vascular calcification in healthy subjects and none of these was designed for that purpose.

In a RCT trial of two years duration in 163 healthy men (age 57±10 years), no difference in calcification of the coronary arteries or the abdominal aorta assessed by computed tomography (CT) was observed between subjects on calcium supplements (1,200 mg/day) and subjects on placebo (Van Pelt et al., 2009). Calcium intakes from diet were not reported.

In contrast, in a retrospective analysis of a two-year RCT of similar size which investigated the effect of supplemental calcium (1,000 mg/day) and vitamin D_3 (20 µg/day) given as fortified milk (*vs.* no supplemental milk) on bone mass in 167 men >50 years of age (Daly et al., 2006), men with

calcification of the abdominal aorta measured by CT at baseline and receiving the fortified milk showed a significantly greater progression of aortic calcification than controls (Daly et al., 2006). Baseline mean dietary calcium intake was about 900 mg/day and serum 25(OH)D was 75 nmol/L.

In the Epidemiology of Coronary Artery Calcification study conducted between 1991 and 2008 (Bhakta et al., 2009), 1,376 randomly selected asymptomatic adults of all ages were repeatedly examined by electron beam computed tomography for coronary artery calcification (CAC) or aortic valve calcification (AVC). A retrospective analysis was performed on the subgroup of 257 participants (144 female) >60 years who had CAC or AVC at baseline and at least one follow-up measurement. None of the males and only 25 of the 144 female subjects reported taking calcium supplements (500-2,000 mg/day). The CAC and AVC scores at baseline or their progression rates over time (mean follow-up 3.7±0.9 years) were not significantly different between calcium supplement female users and non-users. The Panel notes that this study may have been underpowered for the CAC outcome.

The Panel notes that the data available on the relationship between calcium intake and risk of vascular calcification in humans are inconsistent.

A number of large prospective cohort studies have found a positive association between serum calcium concentrations and increased risk of myocardial infarction, stroke or death in the general adult population and in patients with coronary artery disease (Foley et al., 2008; Grandi et al., 2012; Jorde et al., 1999; Lind et al., 1997). However, these studies do not allow conclusions to be drawn on the relationship between dietary calcium intakes and cardiovascular disease (CVD) risk because calcium intakes were not reported.

A systematic review (Chung et al., 2009) which investigated the relationship between calcium intakes (food and supplements) and incidence of cardiovascular (CV) disease (i.e., total, fatal and non-fatal CV events; total, fatal and non-fatal myocardial infarction and stroke) identified ten longitudinal cohort studies (Al-Delaimy et al., 2003; Ascherio et al., 1998; Bostick et al., 1999; Iso et al., 1999; Larsson et al., 2008; Marniemi et al., 2005; Umesawa et al., 2006; 2008; Van der Vijver et al., 1992; Weng et al., 2008), one nested case-control study (Ross et al., 1997), and no RCTs which had evaluated such a relationship. Except for two studies with a sample size of 755 (Marniemi et al., 2005) and 1,340 (Van der Vijver et al., 1992) subjects, the cohorts included >17,700 and up to about 44,000 subjects. Baseline calcium intakes were assessed by FFQs in all studies and were analysed as predictors of long-term cardiovascular outcomes. Calcium intake within the studied populations varied widely across studies. Mean intakes in the lowest and highest quintiles ranged from about 250 and 667 mg/day in the Japan Collaborative Cohort (JACC) Study (Umesawa et al., 2006) to 876 and 1,916 mg/day in a Finnish male cohort (Larsson et al., 2008). Calcium intakes in studies on Asian populations were generally low (Umesawa et al., 2006; 2008; Weng et al., 2008). Two studies addressed CV death in men and women separately with follow-ups of 9 and 28 years (Umesawa et al., 2006; Van der Vijver et al., 1992); three studies assessed cardiac events (fatal and non fatal combined) either in both sexes together or in men with follow-ups of 10-13 years (Al-Delaimy et al., 2003; Marniemi et al., 2005; Umesawa et al., 2008); cardiac death was analysed in four studies, separately in men and women, at 8, 9, 12 or 28 years of follow-up (Al-Delaimy et al., 2003; Bostick et al., 1999; Umesawa et al., 2008; Van der Vijver et al., 1992), and non-fatal cardiac events in one study in men with 12 years of follow-up (Al-Delaimy et al., 2003); six studies assessed total incidence of stroke in men, women, or both sexes combined with follow-ups of 8-14 years (Ascherio et al., 1998; Iso et al., 1999; Larsson et al., 2008; Marniemi et al., 2005; Umesawa et al., 2008; Weng et al., 2008); and two studies addressed fatal stroke in men and women separately with follow-ups of 10 and 13 years (Ross et al., 1997; Umesawa et al., 2006). One study (the Iowa Women's Health Study, Bostick et al., 1999) found a significant association between calcium intake <696 mg/day and higher risk of ischemic heart disease death compared to an intake of >1,425 mg calcium/day in white women aged 55 to 69 years. A Japanese (Umesawa et al., 2008) and a Taiwanese (Weng et al., 2008) study in men and women (40-79 years and ≥40 years, respectively) found progressively lower risks for stroke

in subjects in higher quintiles of calcium intake in populations with relatively low calcium intakes, whereas one study in women (32-57 years) found significantly higher stroke risk in subjects with calcium intake <500 mg/day compared with women in the next two higher quintiles (Iso et al., 1999). No other associations between calcium intake (total, from food or from supplements) and risk of CVD (any outcome, men, women, or both sexes combined) were reported.

Three additional prospective cohort studies on the relationship between calcium intakes and risk of CVD have been published.

In the Kuopio Osteoporosis Risk Factor and Prevention Study (Pentti et al., 2009), 10,555 females aged 52-62 years without coronary heart disease (CHD) in 1994 were followed-up for seven years. Information about health events and supplemental calcium intake was obtained at baseline via questionnaires, whereas dietary calcium intakes were calculated from liquid milk products and cheese. Dietary calcium intakes in the 2,723 (25.8 %) users and the 7,832 non-users of calcium or calcium plus vitamin D supplements according to the 1994 questionnaire were 773±351 mg/day and 818±404 mg/day, respectively. In age-adjusted analysis of the entire cohort, the hazard ratio (HR) for CHD was 1.14 (95 % CI 0.94–1.39) in calcium supplement users compared with non-users. The multivariate adjusted HR for supplement users compared to non users with respect to CHD was 1.24 (95 % CI 1.02-1.52) for the total sample and 1.26 (95 % CI 1.01-1.57) for postmenopausal women. The Panel notes that calcium intakes from supplements were not reported.

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study (Li et al., 2012), 23,980 participants aged 35-64 years with no history of major CV events were followed up for about 11 years. Dietary calcium was assessed at baseline using a FFQ, whereas use of dietary supplements (including calcium) was checked by questionnaires at baseline and regularly during follow-up. Outcome measures were incidence of myocardial infarction, incidence of stroke, and CVD mortality. A total of 354 cases of myocardial infarction, 260 cases of stroke and 267 cases of CV death were documented during follow-up. Between 3 and 4 % of participants reported use of calcium supplements (either alone or in combination with other vitamins and minerals), but doses of supplemental calcium were not reported. Mean dietary calcium intake at baseline was 766 mg/day in supplement non-users and about 820 mg/day in supplement users. After adjustment for potential confounders, none of the linear trend tests were statistically significant. A statistically significant inverse association was only found between total dietary calcium intake and risk of myocardial infarction for the third (820 mg/day) quartile compared with the lowest (513 mg/day) quartile (HR 0.69; 95 % CI 0.50-0.94) in both sexes combined. The association was also significant for women (HR 0.43; 95 % CI 0.22-0.82), but not for men. Users of calcium supplements had a statistically significantly increased risk of myocardial infarction in comparison with non-users of any supplements (HR 1.86; 95 % CI 1.17-2.96). This association was more pronounced for calcium-only supplement users (HR 2.39; 95 % CI 1.12-5.12), and related to most recent but not to cumulative calcium supplementation. No significant association was found between calcium supplementation and risk of either stroke or overall CVD mortality.

In a subsequent publication (Mursu et al., 2011) of the Iowa Women's Health Study (Bostick et al., 1999), 38,772 women aged 55-69 years were followed-up for 19 years. Diet was assessed using a FFQ in 1986 and 2004, and the use of supplemental calcium by a specific questionnaire in 1986, 1987, 1989, 1992, 1997 and 2004. After adjustment for confounders, use of calcium-containing supplements was associated with a significantly lower rate of total mortality (HR 0.91; 95 % CI 0.88-0.94) and cardiovascular mortality (HR 0.87; 95 % CI 0.82-0.92). The inverse association between supplemental calcium and total mortality was not significant at the highest doses of supplemental calcium (>1,300 mg calcium/day). The Panel notes that dietary (and thus total) calcium intakes were not reported in this follow-up analysis.

The Panel notes that calcium intakes up to about 2,000 mg/day from food and supplements have not generally been associated with an increased risk of CV events in a high number of large prospective cohort studies.

No RCTs specifically designed to investigate the effects of supplemental calcium on CVD risk are available.

In a systematic review and meta-analysis (Wang et al., 2010), four RCTs which reported on the occurrence of CV events with calcium supplementation versus placebo were identified (Baron et al., 1999; Bolland et al., 2008; Prince et al., 2006; Reid et al., 2008). The study by Baron et al., (1999) reported similar proportions of subjects hospitalised for cardiac disease (10 % *vs.* 11 %) or stroke (2 % *vs.* 3 %) among those who received 1,200 mg/day of supplemental calcium (n=464) and those who received placebo (n=466) for four years (mean calcium intakes from diet 880 mg/day). Prince et al., (2006) also found similar rates of CHD in women receiving supplemental calcium (n=730) or placebo (n=730) for five years (mean calcium intakes from diet 915 mg/day). Consumption of calcium supplements (1,000 mg/day; n=732) for five years did not increase the risk of myocardial infarction, stroke or composite CVD endpoint (myocardial infarction, stroke, sudden death) in post-menopausal women (mean calcium intakes from diet 860 mg/day) when unreported events obtained from a national database were included in the analysis (Bolland et al., 2008). One trial in men of two years duration found significantly more self-reported composite CV events in the calcium supplemented group (600 mg or 1,200 mg/day; n=216) than in the placebo group (n=107) (Reid et al., 2008). The Panel notes the low number of cases reported in each group (three in the calcium and one in the placebo groups). The pooled relative risk of CVD for all trials combined was 1.14 (95 % CI 0.92-1.41). The Panel considers that this meta-analysis does not show an increased risk of CV events with calcium supplements of 600 to 1,200 mg/day consumed for two to five years in addition to dietary calcium intakes of about 900 mg/day.

A systematic review and meta-analysis (Bolland et al., 2010) considered 11 double-blind RCTs (Baron et al., 1999; Bolland et al., 2008; Bonithon-Kopp et al., 2000; Bonnick et al., 2007; Dawson-Hughes et al., 1990; Grant et al., 2005; Lappe et al., 2007; Lappe and Heaney, 2008; Prince et al., 2006; Reid et al., 1993, 1995; Reid et al., 2006; Reid et al., 2008; Riggs et al., 1998) which used calcium supplements at doses ≥500 mg/day for more than one year in subjects aged ≥40 years at baseline for the prevention or treatment of osteoporosis or colorectal adenomas. Trials were excluded when calcium plus vitamin D were compared to placebo. The studies included collectively about 12,000 subjects (6,116 in the calcium supplemented groups; 5,805 in the placebo groups) and the outcome measures of interest were myocardial infarction, stroke, sudden death, and death from all causes. Only the four RCTs included in the meta-analysis by Wang et al. (2010) had reported on these outcomes. Baseline age of participants ranged from 56 to 77 years and trial duration from two to five years. Doses of supplemental calcium ranged from 500 to 2,000 mg/day in addition to average dietary calcium intakes of 400-1,240 mg/day. Calcium supplementation did not increase the risk for any outcome in any of the individual studies, or the risk of myocardial infarction, stroke, and sudden death combined, the risk of death, or the risk of stroke in the meta-analyses performed. Allocation to calcium supplementation was associated with an increased risk of myocardial infarction (RR 1.27, 95 % CI 1.01-1.59). One trial (Grant et al., 2005) accounted for 66 % of the subjects and for >50 % of the CV events in the meta-analysis. The compliance rate with the study pills in that study was only 54.5 % (about 45 % in the calcium arms), and the clinical characteristics of participants who did and did not return the completed health questionnaires used for the allocation of events were unknown, which may have introduced bias in between-group comparisons. The Panel notes that cardiovascular events, including myocardial infarction, were not end points in a number of trials but the events were rather attributed on the basis of self-reported health questionnaires and were not verified. The Panel also notes that event frequency and differences in the number of events between the calcium and placebo groups were small, and that the use of multiple end points without adjustment of the level of significance for multiple testing increases the likelihood of chance findings. The Panel considers that

this meta-analysis does not show an increased risk of CV events (myocardial infarction or stroke) with calcium supplements of 500 to 2,000 mg/day consumed for two to five years in addition to dietary calcium intakes of 400-1,240 mg/day.

The same authors (Bolland et al., 2011) updated the above mentioned meta-analysis by including data from two study arms comparing calcium and vitamin D supplements against placebo (Grant et al., 2005; Lappe et al., 2007), and from a sub-sample of subjects participating in the WHI intervention trial (supplementation with calcium and vitamin D versus placebo) described in Section 3.2.2.1. In that study, no effect of calcium (and vitamin D) supplements on confirmed cases of myocardial infarction, stroke, or coronary heart disease death, which were pre-specified secondary efficacy outcomes of the study, had been reported by the authors (Hsia et al., 2007). In subgroup analyses, women with higher total calcium intake (diet plus supplements) at baseline were not at higher risk for coronary events or stroke if assigned to the active calcium/vitamin D group. In the meta-analysis by Bolland et al. (2011), only data from subjects not taking personal supplements at baseline were considered. The Panel notes that the reasons for the selection are unclear, and that subjects were not randomised on the basis of taking personal supplements. The Panel also notes that the additional data considered (supplementation with calcium plus vitamin D against placebo) does not provide information about the risk associated with supplemental calcium intakes *per se*. The Panel considers that this meta-analysis suffers from the same limitations as the previous meta-analysis by the same authors (Bolland et al., 2010), and that it does not provide additional information about the relationship between calcium intakes and risk of CVD.

The Panel considers that long-term calcium intakes from diet and supplements up to 2,500-3,000 mg/day are not associated with an increased risk of cardiovascular disease in adults.

3.2.4. Prostate cancer

The majority of epidemiological studies and the few RCTs which have reported cancer as an outcome found an inverse or no association between calcium intakes from food and/or supplements and the risk of cancer (incidence and mortality), with the exception of prostate cancer (Chung et al., 2009; IoM, 2011; WCRF/AICR, 2007).

The report from the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR, 2007), reviewed nine prospective cohort studies (Baron et al., 2005; Berndt et al., 2002; Chan et al., 2000; Chan et al., 2001; Giovannucci et al., 1998; Laaksonen et al., 2004; Platz et al., 2004; Rodriguez et al., 2003; Schuurman et al., 1999; Tseng et al., 2005), 12 case-control studies (Chan et al., 1998; Du et al., 1997; Hayes et al., 1999; Hodge et al., 2004; Kaul et al., 1987; Key et al., 1997; Ohno et al., 1988; Oishi et al., 1988; Ramon et al., 2000; Tavani et al., 2001; Tavani et al., 2005; Tzonou et al., 1999; Vlajinac et al., 2001; Vlajinac et al., 1997; Walker et al., 2005) and two ecological studies (Boing et al., 1985; Liaw et al., 2003) which investigated the association between calcium intake and risk of prostate cancer. A positive association between calcium intake and risk of prostate cancer was reported in three cohort studies (Chan et al., 2001; Giovannucci et al., 1998; Tseng et al., 2005), one case-control study (Vlajinac et al., 2001) and one ecological study (Boing et al., 1985), whereas no significant association was observed in the remaining studies. An increased risk of advanced/aggressive prostate cancer was also associated with increased intakes of milk and dairy products in one (Giovannucci et al., 1998; 2006) out of the four cohort studies which reported on this outcome. The WCRF/AICR (2007) concluded that there was a "probable" association between diets high in calcium and prostate cancer risk.

Chung et al. (2009) reviewed 12 cohort studies that reported on the association between calcium intake and the risk of prostate cancer (Baron et al., 2005; Chan et al., 2001; Giovannucci et al., 2006; Koh et al., 2006; Kurahashi et al., 2008; Mitrou et al., 2007; Park et al., 2007a; 2007b; Rodriguez et al., 2003; Rohrmann et al., 2007; Schuurman et al., 1999; Tseng et al., 2005). The incidence of prostate cancer in these studies ranged from 0.008 to 0.10. Total calcium intake ranged from

<500 mg/day to ≥2,000 mg/day and the time between dietary assessment and the diagnosis of prostate cancer varied from 1 to 17 years. Seven studies did not find an association between calcium intake and the risk of prostate cancer (Baron et al., 2005; Koh et al., 2006; Kurahashi et al., 2008; Park et al., 2007a; 2007b; Rohrmann et al., 2007; Schuurman et al., 1999), whereas the remaining five studies reported a higher risk associated with higher (*vs.* lower) calcium intakes. The higher and lower calcium intakes ranged from 921 to >2,000 mg and from 455 to 1,000 mg/day, respectively.

One multicentre RCT (Baron et al., 2005) which investigated the efficacy of calcium supplementation in the prevention of colorectal carcinomas also assessed the risk of prostate cancer as a secondary outcome. Men (mean age 61.8 years) received either 1,200 mg of calcium (n=327) or placebo (n=327) daily for four years and were followed for up to 12 years for prostate cancer diagnosis. Dietary calcium intake at baseline was comparable in the two groups (about 800 mg/day). Over the entire study period, the risk for prostate cancer was not significantly different in the calcium group compared to the placebo (rate ratio, 0.83; 95 % CI 0.52–1.32). Total calcium intakes were not associated with prostate cancer risk.

The Panel notes that a number of case-control (one out of 12) and prospective cohort studies (five out of 12, three of which were of good quality) have reported an increased risk of prostate cancer with total calcium intakes of 1,000 to >2,000 mg/day compared to intakes ranging from 500 to <1,000 mg/day. However, the Panel also notes that these studies were uncontrolled for factors other than calcium and which may have been responsible for the effect, and that the only RCT which reported on this outcome showed no effect of calcium supplementation at doses of 1,200 mg/day (up to about 2,000 mg/day of total calcium) on the risk of prostate cancer.

The Panel considers that long-term calcium intakes from diet and supplements above 2,000 mg/day are not associated with an increased risk of prostate cancer.

3.2.5. Interactions between calcium and dietary minerals

Calcium has been shown to interfere with both iron and zinc absorption in short term trials or single-dose experiments. This effect has not been observed in long-term observational and intervention studies at dietary calcium intakes in the range of current recommendations or at supplemental calcium intakes up to 2,000 mg/day in adults (SCF, 2003).

The Panel notes that no new data have become available since 2003 on this outcome.

4. Dose response assessment and derivation of a Tolerable Upper Intake Level

4.1. Adults

The SCF (2003) based the derivation of a UL for calcium on the evidence of different intervention studies of long duration, some of which were placebo controlled, in which total daily calcium intakes of 2,500 mg from both diet and supplements were tolerated without adverse effects. Because of the abundance of data, the application of an uncertainty factor was considered unnecessary. A UL of 2,500 mg of calcium per day from all sources was proposed for adults, and for pregnant and lactating women.

A number of placebo controlled human intervention studies in adults published since then also show that total daily calcium intakes of 2,500 mg from both diet and supplements are tolerated without adverse effects.

The Panel notes that new case reports have become available on consumption of calcium supplements and the CAS/MAS syndrome. However, the Panel considers that no dose-response relationships can be derived from these.

The Panel considers that no relationship has been established between long-term calcium intakes from diet and supplements and increased risk of nephrolithiasis, cardiovascular disease or prostate cancer.

The Panel proposes a UL of 2,500 mg/day of calcium from all sources.

4.2. Pregnant and lactating women

The UL for pregnant and lactating women established by the SCF (2003) was the same as for adults.

The Panel notes that no new data have become available since 2003 for this population subgroup.

The Panel proposes a UL of 2,500 mg/day of calcium from all sources.

4.3. Infants

In 2003, the SCF concluded that the data available were insufficient to establish a UL for infants.

The Panel notes that no new data have become available for this population subgroup since 2003.

The Panel concludes that the data are insufficient to establish a UL for infants.

4.4. Children and adolescents

In 2003, the SCF concluded that the data available were insufficient to establish a UL for children and adolescents.

The Panel notes that calcium intakes of about 1,800 mg/day did not affect renal function in children aged 1-6 years in one small, short-term (three month) RCT (Markowitz et al., 2004). However, the Panel considers that these data are not sufficient for establishing a UL for children or adolescents.

The Panel concludes that the data are insufficient to establish a UL for children or adolescents.

5. Characterisation of the risk

Data from European populations indicate that intakes of calcium in high consumers among adult males can be close to the UL.

Although available data do not allow the setting of a UL for infants, children or adolescents, no risk has been identified with highest current levels of calcium intake in these age groups.

CONCLUSIONS

The Panel proposes a UL for calcium of 2,500 mg for adults, and for pregnant and lactating women. The Panel considers that the available data are insufficient to set a UL for infants, children or adolescents.

Data from European populations indicate that intakes of calcium in high consumers among adult males can be close to the UL. Although available data do not allow the setting of a UL for infants,

children or adolescents, no risk has been identified with highest current levels of calcium intake in these age groups.

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APPENDICES

A. INTAKE OF CALCIUM AMONG ADULTS IN EUROPEAN COUNTRIES

Nutrient source	Sex	Country	References	Dietary method	n		Age min		Age max	Population / Fortified foods included or excluded	mean	median	P75	P95	P97.5
Food	**Women**	**Austria**	(Elmadfa et al., 2009)	24-hour recall	426	<	25	>	35	pregnant 2nd trimester	919.0				
					76	<	25		25	pregnant 2nd trimester	798.0				
					288		25		35	pregnant 2nd trimester	919.0				
					62		35	>	35	pregnant 2nd trimester	1,078.0				
		Denmark	(Pedersen et al., 2010)	7-day record (data collected in 2003-2008)	150		18		24		1,040.0			1,619.0	
					340		25		34		1,106.0			1,843.0	
					412		35		44		1,058.0			1,787.0	
					359		45		54		961.0			1,585.0	
					326		55		64		926.0			1,559.0	
					198		65		75		880.0			1,582.0	
			(Tetens et al., 2011)	7-day record and interview (data collected in 2000-2004)	671		18		49	Non supplement users	939.0			1,675.0	
					825		18		49	Supplements users	1,014.0			1,712.0	
					280		50		75	Non supplement users	834.0			1,524.0	
					599		50		75	Supplements users	864.0			1,589.0	
		Finland	(Paturi et al., 2008)	48-hour recall and two 3-day records for the usual intakes over the past year (assessment of underreporters)	641		25		74	Usual intakes. Underreporters excluded	1,000.0			1,700.0	
		Germany	(MRI, 2008)	24-hour recall + Dietary History	510		19		24		1,039.0			1,756.0	
					972		25		34		1,061.0			1,804.0	
					2,694		35		50		1,067.0			1,815.0	
					1,840		51		64		1,011.0			1,700.0	
					1,562		65		80		918.0			1,553.0	
		Ireland	(IUNA (Irish Universities Nutrition Alliance), 2011)	4-day record	255		18		35		772.0			1,388.0	1,590.0
					232		36		50		775.0			1,289.0	1,436.0
					153		51		64		782.0			1,226.0	1,397.0

Nutrient source	Sex	Country	References	Dietary method	n	Age min		Age max	Population / Fortified foods included or excluded	mean	median	P75	P95	P97.5
Food	**Women**	**Italy**	(Sette et al., 2010)	Consecutive 3-day food record	1,245	18	<	65	Including fortified food	730.0			1,233.0	
					316	65		99	Including fortified food	754.0			1,285.0	
		Poland	(Flynn et al., 2009)	24-hour recall	1,656	18		96		516.0			1,113.0	
		Spain	(Flynn et al., 2009)	Two non-consecutive 24-hour recalls (one for all, a second for 62 % of the sample)	895	18		64	Data collected in Catalonia	767.0			1,045.0	
		Sweden	(Becker and Pearson, 2002)	7-day record	67	17		24		937.0			1,436.0	
					128	25		34		973.0			1,421.0	
					143	35		44		888.0			1,362.0	
					118	45		54		901.0			1,451.0	
					68	55		64		927.0			1,607.0	
					65	65		74		937.0			1,504.0	
		The Netherlands	(van Rossum et al., 2011)	Two non-consecutive 24-hour dietary recalls	347	19		30			910.0		1,482.0	
					351	31		50			953.0		1,540.0	
					353	51		69		,	985.0		1,583.0	
Food	**Men**	**Denmark**	(Pedersen et al., 2010)	7-day record (data collected in 2003-2008)	105	18		24		1,374.0			2,182.0	
					234	25		34		1,235.0			2,071.0	
					318	35		44		1,182.0			1,967.0	
					336	45		54		1,073.0			1,898.0	
					336	55		64		955.0			1,742.0	
					240	65		75		952.0			1,669.0	
			(Tetens et al., 2011)	7-day record and interview (data collected in 2000-2004)	663	18		49	non supplement users	1,043.0			1,937.0	
					587	18		49	supplements users	1,125.0			1,931.0	
					363	50		75	non supplement users	829.0			1,492.0	
					491	50		75	supplements users	859.0			1,639.0	
		Finland	(Paturi et al., 2008)	48-hour recall and two 3-day records for the usual intakes over the past year (assessment of underreporters)	637	25		74	Usual intakes. Underreporters excluded	1,286.0			2,000.0	

Nutrient source	Sex	Country	References	Dietary method	n	Age min		Age max	Population / Fortified foods included or excluded	mean	median	P75	P95	P97.5
Food	**Men**	**Germany**	(MRI, 2008)	24-hour recall + Dietary History	510	19		24		1,281.0			2,422.0	
					690	25		34		1,252.0			2,226.0	
					2,079	35		50		1,167.0			2,109.0	
					1,633	51		64		1,071.0			1,908.0	
					1,469	65		80		970.0			1,669.0	
		Ireland	(IUNA (Irish Universities Nutrition Alliance), 2011)	4-day record	276	18		35		1,105.0			1,856.0	2,091.0
		Ireland	(IUNA (Irish Universities Nutrition Alliance), 2011)	4-day record	205	36		50		1,023.0			1,836.0	2,103.0
					153	51		64		957.0			1,589.0	1,812.0
		Italy	(Sette et al., 2010)	Consecutive 3-day food record	1,068	18	<	65	Including fortified food	799.0			1,433.0	
					202	65		99	Including fortified food	825.0			1,403.0	
		Poland	(Flynn et al., 2009)	24-hour recall	1,324	18		96		658.0			1,428.0	
		Spain	(Flynn et al., 2009)	Two non-consecutive 24-hour recalls (one for all, a second for 62 % of the sample)	718	18		64	Data collected in Catalonia.	821.0			1,203.0	
		Sweden	(Becker and Pearson, 2002)	7-day record	67	17		24		1,201.0			2,073.0	
					128	25		34		1,090.0			1,719.0	
					143	35		44		1,029.0			1,638.0	
					118	45		54		1,041.0			1,657.0	
					68	55		64		1,035.0			1,699.0	
					65	65		74		1,064.0			1.868.0	
		The Netherlands	(van Rossum et al., 2011)	Two non-consecutive 24-hour dietary recalls	356	19		30			1,080.0		1,777.0	
					348	31		50			1,136.0		1,852.0	
					351	51		69			1,099.0		1,803.0	

Nutrient source	Sex	Country	References	Dietary method	n	Age min		Age max	Population / Fortified foods included or excluded	mean	median	P75	P95	P97.5
Food	**Men and women**	**Belgium**	(De Vriese et al., 2006)	Two 24-hour recall	873	19		59		813.3		978.0		
					822	60		74		695.4		847.0		
					744	75	>	75		623.7		755.0		
		France	(Dufour et al., 2010)	7-day record	1,918	18		79	Non under-reporters. Without fortified food.	913.1			1,487.5	1,652.0
		Ireland	(IUNA (Irish Universities Nutrition Alliance), 2011)	4-day record	226	65	>	65		840.0			1,518.0	1,654.0
		Portugal	(Lopes et al., 2006)	Food frequency questionnaire	478	18		39	Data collected in Porto	1,027.3			1,714.3	
					537	40		49		915.1			1,600.7	
					789	50		64		922.6			1,629.3	
					585	65	>	65		882.8			1,514.7	
		United Kingdom	(Bates et al., 2011)	4-day record	807	19		64		830.0				1,542.0
					224	65	>	65		871.0				1,630.0
Supplements	**Women**	**Austria**	(Elmadfa et al., 2009)	Quantitative consumption frequency questionnaire	28	18		65	Assessment of the consumption of supplements among 282 adults in all Austria (77 supplement users)		200.0	353.0		
		Germany	(MRI, 2008)	24-hour recall + Dietary History	40	19		24	Users of calcium supplements	288.0			500.0	
					84	25		34	Users of calcium supplements	198.0			500.0	
					285	35		50	Users of calcium supplements	272.0			800.0	
					324	51		64	Users of calcium supplements	353.0			1,000.0	
					338	65		80	Users of calcium supplements	409.0			1,200.0	

Nutrient source	Sex	Country	References	Dietary method	n	Age min	Age max	Population / Fortified foods included or excluded	mean	median	P75	P95	P97.5
Supplements	**Men**	**Austria**	(Elmadfa et al., 2009)	Quantitative consumption frequency questionnaire	21	18	65	Assessment of the consumption of supplements among 282 adults in all Austria (77 supplement users)		162.0	341.0		
		Germany	(MRI, 2008)	24-hour recall + Dietary History	38	19	24	Users of calcium supplements	188.0			500.0	
					53	25	34	Users of calcium supplements	203.0			620.0	
					152	35	50	Users of calcium supplements	236.0			600.0	
					146	51	64	Users of calcium supplements	245.0			620.0	
					182	65	80	Users of calcium supplements	319.0			1,200.0	
Food and supplements	**Women**	**Denmark**	(Tetens et al., 2011)	7-day record and interview (data collected in 2000-2004)	825	18	49	Supplements users	1,130.0			1,881.0	
					599	50	75	Supplements users	1,018.0			1,899.0	
		Finland	(Paturi et al., 2008)	48-hour recall and two 3-day records for the usual intakes over the past year (assessment of underreporters)	641	25	74	Usual intakes. Underreporters excluded	1,190.0			1,830.0	
		Ireland	(IUNA (Irish Universities Nutrition Alliance), 2011)	4-day record	255	18	35		794.0			1,394.0	1,655.0
					232	36	50		824.0			1,394.0	1,702.0
					153	51	64		874.0			1,630.0	1,842.0
		Poland	(Flynn et al., 2009)	24-hour recall	1,656	18	96		523.0			1,121.0	
		Spain	(Flynn et al., 2009)	Two non-consecutive 24-hour recalls (one for all, a second for 62 % of the sample)	895	18	64	Including fortified food. Data collected in Catalonia.	779.0			1,069.0	
		The Netherlands	(van Rossum et al., 2011)	Two non-consecutive 24-hour dietary recalls	347	19	30			918.0		1,501.0	
					351	31	50			983.0		1,602.0	
					353	51	69			1,026.0		1,686.0	

Nutrient source	Sex	Country	References	Dietary method	n	Age min		Age max	Population / Fortified foods included or excluded	mean	median	P75	P95	P97.5
Food and supplements	**Men**	**Denmark**	(Tetens et al., 2011)	7-day record and interview	587	18		49	Supplements users	1,228.0			2,029.0	
					491	50		75	Supplements users	970.0			1,785.0	
		Finland	(Paturi et al., 2008)	48-hour recall and two 3-day records for the usual intakes over the past year (assessment of underreporters)	637	25		74	Usual intakes. Underreporters excluded	1,300.0			2,100.0	
		Ireland	(IUNA (Irish Universities Nutrition Alliance), 2011)	4-day record	276	18		35		1,122.0			1,877.0	2,091.0
					205	36		50		1,036.0			1,836.0	2,103.0
					153	51		64		981.0			1,600.0	1,830.0
		Poland	(Flynn et al., 2009)	24-hour recall	1,324	18		96		662.0			1,428.0	
		Spain	(Flynn et al., 2009)	Two non-consecutive 24-hour recalls (one for all, a second for 62 % of the sample)	718	18		64	Including fortified food. Data collected in Catalonia	831.0			1,217.0	
		The Netherlands	(van Rossum et al., 2011)	Two non-consecutive 24-hour dietary recalls	356	19		30			1,091.0		1,791.0	
					348	31		50			1,154.0		1,869.0	
					351	51		69			1,109.0		1,818.0	
Food and supplements	**Men and women**	**Ireland**	(IUNA (Irish Universities Nutrition Alliance), 2011)	4-day record	226	65	>	65		954.0			2,106.0	2,337.0
		United Kingdom	(Bates et al., 2011)	4-day record	807	19		64		850.0				1,663.0
					224	65	>	65		902.0				1,677.0

NB: white: less than ~50 years. grey: over ~50 years

B. INTAKE OF CALCIUM AMONG CHILDREN IN EUROPEAN COUNTRIES

Nutrient source	Sex	Country	Reference	Dietary method	n	Age min		Age max	Population / Fortified foods included or excluded	mean	median	P75	P90	P95	P97.5
Food	**Boys and girls**	**The Netherlands**	(de Boer et al., 2006)	2-day record (independent days)	333	0.75		0.75	Including fortified food	730.0		812.0	915.0		
					306	1		1	Including fortified food	824.0		938.0	1,085.0		
Food and supplements	**Girls**	**Finland**	(Kyttälä et al., 2008; 2010)	3-day record	198	1		1	non breast-fed infants genetically at-risk of type 1 diabetes	696.0		885.0			
Food and supplements	**Boys**	**Finland**	(Kyttälä et al., 2008; 2010)	3-day record	257	1		1	non breast-fed infants genetically at-risk of type 1 diabetes	670.0		886.0			
Food	**Girls**	**Denmark**	(Andersen et al., 1996)	7-day record	149	1		3		996.0				1,325.0	
		The Netherlands	(Ocke et al., 2008)	2-day record (independent days)	313	2		3		734.0				1,089.0	
Food	**Boys**	**Denmark**	(Andersen et al., 1996)	7-day record	129	1		3		910.0				1,359.0	
		The Netherlands	(Ocke et al., 2008)	2-day record (independent days)	327	2		3		788.0				1,180.0	
Food	**Boys and girls**	**Greece**	(Manios et al., 2008)	3-day record (weighed food records and 24 h recall or food diaries)	2,317	1		5	Non under-reporters. Possible inclusion of supplements not mentioned	1,024.0			1,392.0		
		Italy	(Sette et al., 2010)	Consecutive 3-day food records	52	0	<	3	Including fortified food	664.0				1,070.0	
		The Netherlands	(de Boer et al., 2006)	2-day record (independent days)	302	1.5		1.5	Including fortified food	866.0			1,082.0		
		United Kingdom	(Bates et al., 2011)	4-day food diary	219	1.5		3		773.0					1,365.0
Food and supplements	**Girls**	**Finland**	(Kyttälä et al., 2008; 2010)	3-day record	118	2		2	Children genetically at-risk for type 1 diabetes	870.0		1,019.0			
					235	3		3		881.0		1,062.0			
		The Netherlands	(Ocke et al., 2008)	2-day record (independent days)	313	2		3		740.0				1,099.0	

Nutrient source	Sex	Country	Reference	Dietary method	n	Age min		Age max	Population / Fortified foods included or excluded	mean	median	P75	P90	P95	P97.5
Food and supplements	**Boys**	**Finland**	(Kyttälä et al., 2008; 2010)	3-day record	112	2		2	Children genetically at-risk for type 1 diabetes	844.0		1,037.0			
					236	3		3		925.0		1,109.0			
		The Netherlands	(Ocke et al., 2008)	2-day record (independent days)	327	2		3		795.0				1,184.0	
Food and supplements	**Boys and girls**	**United Kingdom**	(Bates et al., 2011)	4-day food diary	219	1.5		3		775.0					1,365.0
Food	**Girls**	**Ireland**	(IUNA (Irish Universities Nutrition Alliance), a)	7-day record	301	5		12		804.0				1,274.0	1,434.0
		The Netherlands	(van Rossum et al., 2011)	Two non-consecutive 24-hour dietary recalls	151	7		8			817.0			1,353.0	
					352	9		13			846.0			1,393.0	
Food	**Boys**	**Ireland**	(IUNA (Irish Universities Nutrition Alliance), a)	7-day record	293	5		12		907.0				1,488.0	1,578.0
		The Netherlands	(van Rossum et al., 2011)	Two non-consecutive 24-hour dietary recalls	153	7		8			878.0			1,495.0	
					351	9		13			943.0			1,587.0	
Food	**Boys and girls**	**Denmark**	(Pedersen et al., 2010)	7-day record	903	4		14		1,072.0				1,776.0	
		Italy	(Sette et al., 2010)	Consecutive 3-day food records	52	3	<	10	Including fortified food	749.0				1,197.0	
		Germany	(Flynn et al., 2009)	3-day record	1,234	6		11		870.0				1,352.0	
		Poland	(Flynn et al., 2009)	24-hour recall	455	4		10		595.0				1,134.0	

Nutrient source	Sex	Country	Reference	Dietary method	n	Age min	Age max	Population / Fortified foods included or excluded	mean	median	P75	P90	P95	P97.5
Food	**Boys and girls**	**Spain**	(Flynn et al., 2009)	24-hour recall and food frequency questionnaire, a second 24-hour recall in 25-30 % of the sample	723	4	10		867.0				1,123.0	
		The Netherlands	(Flynn et al., 2009)	2-day record (independent days)	639	4	6	Including fortified food	716.0				1,155.0	
		United Kingdom	(Bates et al., 2011)	4-day food diary	423	4	10		804.0					1,339.0
Food and supplements	**Girls**	**Finland**	(Kyttälä et al., 2008; 2010)	3-day record	247	4	4	Children genetically at-risk for type 1 diabetes	930.0		1,089.0			
					349	6	6		991.0		1,172.0			
		The Netherlands	(van Rossum et al., 2011)	Two non-consecutive 24-hour dietary recalls	151	7	8			852.0			1,408.0	
					352	9	13			856.0			1,418.0	
Food and supplements	**Boys**	**Finland**	(Kyttälä et al., 2008; 2010)	3-day record	307	4	4	Children genetically at-risk for type 1 diabetes	983.0					
					364	6	6		1,103.0					
		The Netherlands	(van Rossum et al., 2011)	Two non-consecutive 24-hour dietary recalls	153	7	8			892.0			1,505.0	
					351	9	13			964.0			1,623.0	
Food and supplements	**Boys and girls**	**Germany**	(Flynn et al., 2009)	3-day record	1,234	6	11		874.0				1,352.0	
		Ireland	(IUNA (Irish Universities Nutrition Alliance), a)	7-day record	594	5	12		862.0				1,433.0	
		Poland	(Flynn et al., 2009)	24-hour recall	455	4	10		598.0				1,134.0	

Nutrient source	Sex	Country	Reference	Dietary method	n	Age min		Age max	Population / Fortified foods included or excluded	mean	median	P75	P90	P95	P97.5
Food and supplements	**Boys and girls**	**Spain**	(Flynn et al., 2009)	24-hour recall and food frequency questionnaire, a second 24-hour recall in 25-30 % of the sample	723	4		10	Including fortified food	898.0				1,151.0	
		Sweden	(Enghardt-Barbieri et al., 2006)	4-day record	590	4		4		855.0				1,330.0	
					889	8		9		959.0				1,537.0	
					1,016	11		12		878.0				1,519.0	
		The Netherlands	(Flynn et al., 2009)	2-day record (independent days)	639	4		6		724.0				1,165.0	
					639	4		6	Including fortified food	811.0				1,247.0	
		United Kingdom	(Bates et al., 2011)	4-day food diary	423	4		10		804.0					1,339.0
Food	**Girls**	**Denmark**	(Pedersen et al., 2010)	7-day record	134	14		17		966.0				1,699.0	
		Ireland	(IUNA (Irish Universities Nutrition Alliance), b)	7-day record	217	13		17		734.0				1,376.0	1,554.0
		Italy	(Sette et al., 2010)	Consecutive 3-day food records	139	10	<	18	Including fortified food	770.0				1,306.0	
		The Netherlands	(van Rossum et al., 2011)	Two non-consecutive 24-hour dietary recalls	354	14		18			876.0			1,435.0	

Nutrient source	Sex	Country	Reference	Dietary method	n	Age min		Age max	Population / Fortified foods included or excluded	mean	median	P75	P90	P95	P97.5
Food	**Boys**	**Denmark**	(Pedersen et al., 2010)	7-day record	101	14		17		1,288.0				2,245.0	
		Ireland	(IUNA (Irish Universities Nutrition Alliance), b)	7-day record	224	13		17		1,063.0				1,905.0	2,047.0
		Italy	(Sette et al., 2010)	Consecutive 3-day food records	108	10	<	18	Including fortified food	892.0				1,435.0	
		The Netherlands	(van Rossum et al., 2011)	Two non-consecutive 24-hour dietary recalls	352	14		18			1,010.0			1,679.0	
Food	**Boys and girls**	**Belgium**	(De Vriese et al., 2006)	Two 24-hour recall	806	15		18		787.9		966.0			
		Germany	(Flynn et al., 2009)	3-day record	1,272	12		17		1,337.0				2,400.0	
		Spain	(Flynn et al., 2009)	24-hour recall and food frequency questionnaire, a second 24-hour recall in 25-30 % of the sample	1,137	11		17		878.0				1,231.0	
		United Kingdom	(Bates et al., 2011)	4-day food diary	453	11		18		785.0					1,522.0
Supplements	**Girls**	**Germany**	(MRI, 2008)	24-hour recall + Dietary History	34	14		18		189.0				1,000.0	
Supplements	**Boys**	**Germany**	(MRI, 2008)	24-hour recall + Dietary History	43	14		18		189.0				500.0	
Food and supplements	**Girls**	**The Netherlands**	(van Rossum et al., 2011)	Two non-consecutive 24-hour dietary recalls	354	14		18			872.0			1,433.0	
Food and supplements	**Boys**	**The Netherlands**	(van Rossum et al., 2011)	Two non-consecutive 24-hour dietary recalls	352	14		18			1,010.0			1,692.0	

Nutrient source	Sex	Country	Reference	Dietary method	n	Age min	Age max	Population / Fortified foods included or excluded	mean	median	P75	P90	P95	P97.5
Food and supplements	**Boys and girls**	**Germany**	(Flynn et al., 2009)	3-day record	1,272	12	17		1,350.0				2,422.0	
					1,272	12	17	Including fortified food	1,396.0				2,515.0	
		Ireland	(IUNA (Irish Universities Nutrition Alliance), b)	7-day record	441	13	17		906.0				1,657.0	
		Poland	(Flynn et al., 2009)	24-hour recall	581	11	17		1,398.0				2,975.0	
		Spain	(Flynn et al., 2009)	24-hour recall and food frequency questionnaire, a second 24-hour recall in 25-30 % of the sample	1,137	11	17	Including fortified food	900.0				1,267.0	
		United Kingdom	(Bates et al., 2011)	4-day food diary	453	11	18		786.0					1,522.0

NB: First white section: infants. First grey section: ~1-3 years. Second white section: older children. Second grey section: ~teenagers

GLOSSARY AND ABBREVIATIONS

1,25-$(OH)_2$-D	1,25-dihydroxycholecalciferol
25(OH)D	25-Hydroxy-vitamin D
AVC	Aortic valve calcification
BMI	Body Mass Index
CAC	Coronary artery calcification
CAS	Calcium-alkali-syndrome
CaSR	Calcium-sensing receptor
CHD	Coronary heart disease
CI	Confidence interval
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
CYP	Cytochrome
PEPIC	European Prospective Investigation into Cancer and Nutrition
FFQ	Food frequency questionnaire
HR	Hazard ratio
IoM	Institute of Medicine
IU	International Unit
JACC	Japan Collaborative Cohort
LOAEL	Lowest-observed-adverse-effect-level
MAS	Milk-alkali syndrome
NCX1	Na/Ca Exchanger 1
NOAEL	No observable adverse effect level
OMIM	Online Mendelian Inheritance in Man
PMCA	Plasma-membrane Ca-ATPase
PTH	Parathyroid hormone

RCT	Randomised controlled trial
RR	Relative risk
SCF	Scientific Committee on Food
TRPV	Transient Receptor Potential Vanilloid
UL	Tolerable Upper Intake Level
VDR	Vitamin D receptor
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research
WHI	Women's Health Initiative